Research Opportunity Announcement OTA-21-015J

RECOVER PASC PATHOBIOLOGY SUBSTUDIES

1. Introduction

The NIH is soliciting applications in support of the goals of the Researching COVID to Enhance Recovery (RECOVER) Initiative, which seeks to understand, diagnose, treat, and prevent post-acute sequelae of SARS-CoV-2 infection (PASC). This Research Opportunity Announcement focuses on studies that will rapidly advance understanding of the biologic mechanisms underpinning the clinical phenotypes and symptoms of PASC by analyses performed on biospecimens collected within the RECOVER adult, pediatric and autopsy cohorts. Applicants to this ROA opportunity must be investigators at sites already supported under the RECOVER consortium under an existing OT agreement. Investigators at sites under the RECOVER consortium are able to work with laboratories or investigators outside of the RECOVER Consortium in order to meet critical research needs or bring in expertise which may not be available at the site carrying the OT agreement.

Recovery from SARS-CoV-2 infection is variable, with many patients recovering quickly while others experience longer-term post-acute sequelae. The magnitude of the public health impact of these sequelae is currently unknown but potentially very large given the number of individuals who have been and will be infected. Thus, it is a public health priority to understand and develop strategies to prevent and treat PASC.

Accordingly, the goal of the RECOVER PASC Initiative is to rapidly improve understanding of recovery after SARS-CoV-2 infection and to prevent and treat PASC. Toward these ends, the Initiative is designed to address two overarching scientific objectives:

1. Define the biological mechanisms underlying pathogenesis of the sequelae of SARS-CoV-2 infection occurring >30 days after index infection.
2. Link these mechanisms to the incidence, prevalence and sequelae to SARS-CoV-2 infection occurring >30 days after index infection including studies that address the spectrum of clinical symptoms, multi-organ dysfunction and distinct phenotypes identified in PASC.

2. Research Objectives

To further improve our understanding of the clinical manifestations of PASC and the mechanisms leading to the various symptoms, dysfunction of multiple organs and biologic systems, and phenotypes seen in PASC patients, the NIH encourages the submission of substudies to the RECOVER cohorts to support these goals.

In addition to the topics funded through the original RECOVER protocols and the previous pathobiology 45 ROA and NOSI projects, RECOVER also intends to implement the substudy described below. NIH will prioritize applications that complement previously funded and planned projects and high-priority research areas indicated in this announcement. Applicants for this highly competitive program should propose cross-disciplinary and collaborative research teams to address their proposed hypotheses. Applicants are encouraged to reach out to the RECOVER Administrative Coordinating Center (ACC) at RECOVERreviews@rti.org and the NIH at RECOVERPathBio@nih.gov prior to submission if proposals plan to cover any of topics previously funded or those noted below:

A comprehensive, longitudinal, multi-omics systems biology substudy is under development to enable investigation of mechanisms of PASC and PASC subtypes across adults and children.

Research <u>proposals are *strongly encouraged* in the following topic areas</u>, alone or in combination (this list may be updated as new research and needs emerge):

- Viral persistence/reactivation as a potential cause of some PASC subtypes
- Chronic immune dysfunction as a potential cause of some PASC subtypes
- Comparative studies of PASC with other post-viral and post-infectious syndromes
- Studies of vascular injury, thrombosis, and other related potential mechanisms of PASC (e.g. complement pathway dysfunction)
- Advanced imaging analysis, e.g., AI/ML, to define the long term impact of COVID on organ structure/function and characterize PASC phenotypes
- Linking autopsy findings with pathobiological mechanisms of PASC to guide targeted interventions
- Effect of reinfection and/or emerging variants on the risk for PASC
- Intersectionality of social determinants of health, built environments and/or pre-existing conditions prior to acute infection and the risk for development or severity of PASC
- Remaining gaps in tissue-specific manifestations of PASC including molecular mechanism such as dysregulation or disruption of normal physiologic pathways (reduction in serotonin, mitochondrial or bioenergetic cellular functions), correlating abnormal MRI findings in the brain, heart and lung to pathologic mechanism associated with symptomology in PASC (shortness of breath, cognitive dysfunction, etc.)
- Studies that propose to validate published studies on potential mechanisms of PASC within the framework of the data and biospecimens collected within RECOVER cohorts

Supported research is expected to inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the pathobiological mechanisms and pathways underpinning post-acute sequelae, the molecular mediators of its protean symptomatology, and the possible multiple clinical clusters/sub-phenotypes. Correspondingly, supported research is expected to leverage and build upon—but not duplicate—RECOVER cohort enrollment, samples, and data analyses performed as part of the protocol implementation. Analyses using on-study biospecimens is critical to generating a robust dataset that can inform the underlying mechanisms of response and resistance to infection as well as potential therapeutic avenues. Studies leveraging the autopsy resources and other biospecimen resources, including RECOVER cohorts are welcome. While new data may be generated, proposals for secondary analysis of data previously collected in RECOVER are also encouraged. Proposals with plans to collect additional data and biospecimens must do so within the context of the RECOVER protocols. If necessary, additional samples and data collected outside RECOVER may also be utilized to confirm some of the findings, i.e., outside data used for validation of findings utilizing RECOVER data and biospecimens.

In order to comprehensively address these objectives, high-throughput assays, use of well-established core facilities and multi-omic approaches (i.e., transcriptomics, proteomics, genomics, etc.) are encouraged. Proposed analytic techniques may include a combination of these approaches. Given the wide array of assays, technologies and principles that can be applied, consideration will be given to applications that address fundamental questions associated with understanding the biological mechanisms and pathways involved in SARS-CoV-2 infection and PASC, and its resolution. Pragmatic high-throughput techniques with potential for adaptation to clinical settings are preferred but not required. Applicants must provide a strong scientific rationale for the proposed technology and planned analytic approach with inclusion of preliminary data with appropriate quality controls. Proposals may be structured to permit subcontracting to other laboratories outside of the RECOVER Consortium that are scientifically justified to execute the proposed work and led by the ROA Applicant in order to promote collaboration among RECOVER Investigators as described in Lower Tier Agreements below.

3. Special Award Terms

The complete terms and conditions of each sub-agreement issued under this ROA are subject to negotiation and will be contained in the Other Transactions Agreement entered between RECOVER ACC, on behalf of the NIH, and the Awardee. This Special Award Terms section is provided for informational purposes only in order to provide prospective applicants with an understanding of key expectations and terms that may differ from traditional NIH award mechanisms.

Lower Tier Agreements

Lower tier agreements are permitted and will be considered with strong scientific justification. Funding for lower tier agreements must be included in the applicant budget. These lower tier agreements are intended to allow the Awardee to work with laboratories or investigators outside of the RECOVER Consortium in order to meet critical research needs or bring in expertise which may not be available at the site carrying the OT agreement. These lower tier agreements will be managed by the awardees once approved with funding provided by the NIH.

Publications

Awardees are expected to adhere to the publication guidance inclusive of terminology referencing RECOVER from the RECOVER Presentations and Publications Oversight Committee (PPOC). All publications must reference the OT award number for the individual ROA award and include the following language in the acknowledgements and/or citation of funding section of all accepted publications supported by this program: [INSERT OT#] was supported by the NIH RECOVER Pathobiology Research Program.

Data Sharing

The NIH expects and supports the timely release and sharing of research data from RECOVER supported studies for use by other researchers to expedite the translation of research results into knowledge, products, and procedures to improve human health (https://grants.nih.gov/grants/policy/data_sharing/). The overarching goal of this ROA is to lead to rapid delineation of PASC pathobiology in order to foster progress in diagnostic, therapeutic, and preventive avenues for this condition. To achieve those goals, Awardees must pledge to rapidly share data and biospecimens where it is not prohibited (i.e., Tribal data sovereignty) with the NIH RECOVER (https://recovercovid.org/) data and biospecimen repositories and ultimately with the broader research community.

Award recipients will work closely with RECOVER on data sharing activities to advance the science of PASC research across the country.

Negotiation

NIH reserves the right to:

- Select for negotiation all, some, one, or none of the proposals received in response to this ROA;
- Segregate portions of resulting awards into components and their associated budget and/or milestones that differ from those that have been proposed;
- Accept proposals in their entirety or to select only portions of proposals for award;
- Fund projects in increments and/or with options for continued work at the end of one or more phases, which can consist of more than one milestone;
- Fund projects in increments with options to terminate activities e.g., based on evolving data/needs of the initiative;

- Request additional documentation (certifications, etc.) ; and
- Remove proposers from award consideration should the parties fail to reach a finalized, fully executed agreement, or if the proposer fails to provide requested additional information in a timely manner.

Authority

This Research Opportunity Announcement (ROA) is issued with the goal of establishing an "other transactions" agreement or sub-agreement pursuant to 42 U.S.C. § 285b-3 and 42 U.S.C. § 282(n).

Eligibility

Eligible entities for receipt of funding under this ROA must be either a RECOVER Consortium hub with a fully executed contract with the RECOVER Clinical Science Core (CSC) or a RECOVER enrolling site with a contract executed under an eligible RECOVER CSC hub.

4. Proposal Format and Requirements

This ROA encourages collaborative research between RECOVER teams. RECOVER cohort hubs or a hub's subcontracted enrolling site(s) are encouraged to submit a single application when possible. Research projects with complementary scientific goals should be submitted in a single application as a collaboration among various investigators and sites within the hub. Applications that are collaborative across multiple sites and hubs are also encouraged. However, when the proposed research projects are not complementary, more than one application from a hub and its subcontracted sites will be considered.

The application should clearly and fully demonstrate the proposer's capabilities, knowledge, and experience, and should justify the budget proposed. The application should develop a plan to support analysis and reporting of the projected number of biospecimens based on participant selection criteria and sampling timepoints. The actual number of biospecimens and timepoints used may be reduced or eliminated based on interim analyses, recruitment, or other considerations.

The Project Plan shall be limited to a maximum of 4 pages including figures. Requested appendix items and biosketches must be included and are not applied to the 4-page limit. Other appendix items are not permitted.

Proposals shall include the following required sections:

- Cover Page
- Project Plan
- Appendix with required appendix items budget justification

Each of these sections will be submitted electronically via the REDCap link provided below.

The Cover Page shall include:

A. The proposal title
B. The applicant's:
    i) Legal entity name
    ii) Address and contact information
    iii) SAM UEI # and expiration date
    iv) DUNS # and expiration date
    v) EIN number

C. The name and contact information for the Principal Investigator(s) (maximum 3) and the name and contact information of the RECOVER contact Principal Investigator
D. List of key personnel with titles and affiliations (maximum 10)
E. The name and contact information for the Awardee's Business Official, the person authorized to negotiate and bind the Awardee as a signatory to the Other Transaction agreement.
F. The total cost proposed

The Project Summary (1 page maximum) shall include:

A. PI Name(s)
B. Institution(s)
C. Title of Project (w no space limit)
D. Summary of Research Objectives, Aims and Methods not to exceed 500 words

The Project Plan (4 pages maximum) must address the following five elements:

A. Technical Approach
The proposal must briefly describe how the work of the proposed will be accomplished. Proposers should provide a description of the precise analyses planned, along with any available information about sensitivity and specificity of technologies selected. Preliminary data on feasibility, limits of detection and sample pre-analytic considerations is expected. The analyses proposed must be able to be run on biospecimens collected according to RECOVER protocols. The applicant is expected to be fully familiar with these protocols. This section should also include a project plan with quarterly milestones and deliverables based on the listed objectives for the one year of support.

B. Key Personnel Experience
Proposers must describe experience of key personnel supporting the planning and implementation of activities described in the ROA. Expertise in and support for the development, implementation, and execution of relevant analytic modalities, platforms, and methodologies on biospecimens, imaging procedures, and other examination components (e.g., ECGs, EEGs, etc.) collected in the RECOVER pediatric, adult and autopsy protocols for proposed testing. Please provide biosketches describing key personnel in the appendix. Biosketches should conform to the most recent NIH template requirements and do not count towards the page limits.

C. Management/Staffing Plan
Proposals should detail how the proposer will provide the necessary project administration, organization, and staff to ensure quality control, compliance with ROA expectations, and necessary staffing adjustments. If relevant, proposers must discuss how existing funded project administration, organization, and staff will be leveraged for support of the RECOVER initiative.

D. Past Experience
Proposers should provide examples of prior project experience relevant to research areas described in this ROA. Each example should include the total funding awarded and dates of award, contact information for a sponsor able to serve as a reference, and a brief description of the project itself, including how the project was analogous to the needs identified in this ROA with respect to the critical research area(s) being proposed. Applicants will need to demonstrate prior work with clinical consortia or networks AND competency associated with the analyses being proposed.

E. Data Analysis, Management and Sharing Plan
Proposal should include a robust in-house plan for quality assurance for all assays including data harmonization for batch effects, between differing assays and/or work performed as different research sites, if applicable. Proposals are strongly encouraged to include a strategy

for the transfer and sharing of samples among other sites or laboratories involved in the application, as applicable. Detailed descriptions of the procedures for biospecimen selection and transfer to research site(s), including feasible and effective workflow to permit the sharing of samples released from the PASC Biorepository Core for use in all aspects of the proposal, if a multi-site or multi-laboratory approach is selected. Proposals should provide statistical analysis and data management plans for raw data generated within the framework of the proposed research. Proposers should demonstrate the proposed statistician or statistical analysis team has the skill and experience to evaluate the hypotheses in the specific aims of the proposal. Utilization of biostatistics, data management, and/or bioinformatics core facilities at the hub site is permitted. Plans for data sharing should detail the types of data to be managed and shared, related tools, software and/or code needed to access or analyze the data and plans for data preservation and access as described in the Data Sharing requirements of this ROA.

Application Appendix

The technical plan may be supported with upload of the following required appendix Items (not counting towards page limits):

1. An existing manual of operations from a prior or ongoing externally funded project serving as external core resource or cohort external to RECOVER as described in this ROA, if applicable
2. Key personnel biosketches

The Budget must address the following:

Project periods may not exceed 24 months. The Budget section must provide a realistic, fully justified project period, the budget and cost must reflect the actual needs of the proposal for performing the work specified in the ROA. This section must also include a project timeline and milestones. Proposed budgets should generally not exceed a maximum total direct cost of $500,000 per year. In addition, the maximum total costs should generally not exceed $800,000 per year. A higher proposed budget could be considered if appropriately justified. Requests for capital expenses for instruments or equipment are not permitted under this ROA. The budget and budget justification will be submitted via the REDCap link provided below.

The anticipated start date for funding is June 1, 2024.

5. Review Process

The RECOVER Administrative Coordinating Center will coordinate the review of applications. Proposal review may include, but not be limited to review by NIH subject matter experts and external experts. Consultation with the RECOVER Ancillary Studies Oversight Committee may be obtained to determine if application aligns with the overall goals, aims of RECOVER and is not duplicative of ongoing work. Consultation with the RECOVER Data and Biospecimens Cores may be included to access feasibility (data and sample availability). Prioritization of proposals will be made by the RECOVER Observational Consortium Steering Committee and final funding decisions will be made by NIH.

Review Criteria

Only the review criteria described below will be considered in the review process:

<u>Budget and Period of Support</u>
The RECOVER Substudies Committee and NIH staff will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

Overall Impact

Given that the aim of these awards is to leverage the RECOVER cohorts to make rapid progress in understanding the mechanisms underpinning the manifestations of PASC, including the mechanisms responsible for the multi-organ/system dysfunction leading to the various symptoms of PASC:

- How might the proposed research increase understanding of the molecular pathways that underlie the long-term effects of SARS CoV-2 infection, including its resolution?
- In what way(s) do the applicants have expertise in understanding the clinical manifestations of PASC and similar post-infection disorders that may share clinical manifestations and mechanistic pathways with PASC?
- How are the applicants' hypotheses clinically relevant regarding the pathobiology of PASC, based on experience or expertise in pertinent biological pathways, systems, organs, or diseases?
- To what extent do the applicants have expertise and experience in cross-disciplinary clinical understanding of tissue/organ/system dysfunction caused by other forms of tissue/organ/system injury relevant to multisystem dysfunction in PASC?
- How do the applicants propose to develop cross-disciplinary and collaborative research?
- In what way does the proposed research have the potential to inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the clinical pathogenetic mechanisms of PASC and the identification of associated clinical pathways?
- In what way has the proposed research set forth appropriate methodology and feasible project timelines, milestones, and deliverables?
- How do the applicants propose to rapidly share data and results with the broader research community, including, as appropriate, deposition into dbGaP or BioData Catalyst, and how will they rapidly submit results for publication?

6. Application Submission

The required application information must be entered by the PI or their designee on the form provided at the REDCap link below. A code will be provided for return access to the REDCap form. The completed proposal form must be submitted by an authorized business official via the REDCap link no later than **March 22, 2024 by 5 PM EST**. Applications nonresponsive to terms of this announcement will not be considered for review.

REDCap application submission link:
https://redcapedc.rti.org/recover/surveys/?s=KYPNCYF3NNWPMF7C